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COMPLETE SPECIFICATION.

Preparation of Arylboronic and Diarylborinic Acids and Esters and Anhydrides thereof.

We, "SHELL" RESEARCH LIMITED, a British Company, of St. Helen's Court, Great St. Helen's, London, E.C.3, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

This invention relates to a process for preparing organoboron compounds having one or two aromatic groups attached to the boron atom, each by a carbon-to-boron linkage. These are called arylboronic and diarylboronic compounds respectively and are collectively referred to herein as arylboron compounds.

It has been proposed to prepare phenylboronic acid by a Grignard reaction in which phenyl magnesium bromide is reacted with a boric acid triester in an anhydrous ethereal reaction medium at about -70°C ., followed by hydrolysis of the resulting phenylboronic acid ester to the phenylboronic acid. This process however is not an attractive one for operation on a commercial scale.

According to the present invention, arylboron compounds are prepared by reacting an aryl magnesium chloride with a boric acid triester in a reaction medium comprising an excess of the aryl chloride used to prepare said aryl magnesium chloride, or a hydrocarbon or a mixture of said aryl chloride and hydrocarbon.

The aryl magnesium chloride is derived from a mono- or poly-nuclear aryl chloride which may contain one or more nuclear chlorine atoms and which may contain substituents which do not affect the formation

of the aryl magnesium chloride or its reaction with the boric acid triester, for example, alkyl, alkoxy, aryloxy, aryl, alkaryl or nitro groups or halogen atoms such as fluorine atoms.

The aryl magnesium chloride can be prepared by heating the aryl chloride with the magnesium to a temperature of at least 130°C ., preferably with vigorous stirring. Approximately one equivalent of magnesium is used for each chlorine atom in the aryl chloride.

To facilitate the formation of the aryl magnesium chloride, the magnesium used should be in the form of powder or turnings with a clean unoxidised surface which has been freshly produced or has been preserved by storage in a vacuum or under a dry inert gas such as hydrogen or nitrogen. Suitably, magnesium sheet or rod, free from oil, is shaved below the surface of the aryl halide in the vessel to be used for the reaction. A small quantity of an initiator may be added to promote the formation of the aryl magnesium chloride, for example, a solution of iodine in ethyl bromide, bromobenzene, cuprous chloride, bromide or iodide, aluminium chloride, phosphorus tribromide, an inorganic sulphate, for example, sulphuric acid, an alkali metal sulphate or bisulphate or zinc, copper, ferrous, ferric, mercuric or stannic sulphate, or copper sulphide.

The preparation of the aryl magnesium chloride may be effected by heating the aryl chloride and magnesium together in equivalent proportions in absence of a diluent but the separation of a gelatinous precipitate of the Grignard compound tends to cause difficulties. It is therefore advantageous to

[Price

add a diluent after the aryl magnesium chloride has begun to separate but before the mixture becomes too viscous. The diluent added should not affect adversely the formation of the aryl magnesium chloride or its subsequent reaction with the boric acid triester and preferably should have a boiling point at least equal to that of the aryl chloride used to avoid lowering the reaction temperature. Examples of diluents which may be used are aromatic hydrocarbons, for example, toluene, a xylene or xylene mixture, tetrahydronaphthalene, decahydronaphthalene or an aliphatic hydrocarbon boiling above 100° C. and preferably in the range 130° to 200° C., or a further quantity of the aryl chloride being used in the preparation of the Grignard compound. Preferably, however, an excess, for example, up to 10 molecular proportions, of the aryl chloride being used to prepare the Grignard compound is present at the beginning of the reaction. The formation of the Grignard compound is in general complete in 2 to 24 hours, usually in 4 to 5 hours, depending on the reaction temperature, the activity of the magnesium and the aryl halide used. Thus, when active magnesium is heated with 3 to 4 equivalents of chlorobenzene under reflux, formation of the phenylmagnesium chloride is complete in 5 to 6 hours.

The boric acid triester with which the aryl magnesium chloride is reacted may be derived from an alcohol or a phenol. Advantageously it is derived from an aliphatic alcohol containing from 1 to 5 carbon atoms in the molecule, the tri-*n*-butyl boric acid ester being particularly suitable if high reaction temperatures are used.

The reaction between the aryl magnesium chloride and the boric acid triester is effected in a reaction medium comprising an excess of the aryl chloride used to prepare the aryl magnesium chloride, or a hydrocarbon or a mixture of said aryl chloride and hydrocarbon. Advantageously the reaction medium used is the same as the diluent used in the preparation of the aryl magnesium chloride.

The aryl magnesium chloride and the boric acid triester may be reacted in approximately equimolecular proportions, the product then comprising aryl boronic acid ester usually mixed with some diarylboronic acid ester. By using a moderate excess of the boric acid triester, for example, up to about 30% by weight excess over the stoichiometric amount, the proportion of arylboronic acid ester in the product can be increased and the proportion of borinic acid ester decreased without affecting the total yield of arylboron compound. If more than 30% by weight excess of the triester is used however, the overall yield of arylboron compounds tends to fall. By using the aryl magnesium chloride and boric acid triester in a molecular ratio of

approximately 2 to 1, the diaryl borinic acid ester is formed with only a very small proportion of arylboronic acid ester. The reaction is preferably effected at a temperature in the range 130° to 250° C.

The formation of arylboronic acid ester when reacting the aryl magnesium chloride and boric acid ester in approximately equimolecular proportions is favoured by carrying out the reaction at low temperatures, preferably below -30° C. Thus, when equimolecular amounts of phenyl magnesium chloride and trimethyl borate were reacted in chlorobenzene at -45° C., the yield of phenylboron compounds obtained was 50% of the theoretical amount, the phenylboronic acid ester forming 80% of this. At higher reaction temperatures, the proportion of phenylboronic acid ester progressively decreased and that of the diphenylboronic acid ester progressively increased until the arylboron compounds obtained when the reaction was effected by heating under reflux (about 132° C.) contained only 10 to 15% by weight of phenylboronic acid ester but 39% weight of diphenylboronic acid ester.

The formation of the arylboronic compound at the expense of the diarylboronic compound in the process of the invention is also favoured by gradually adding the aryl magnesium chloride to the boric acid triester, whereby the reaction is for the most part carried out in presence of excess ester. Similarly the formation of the diarylboronic compound is favoured at the expense of the aryl boronic compound by gradually adding the boric acid triester to the aryl magnesium chloride, whereby the reaction is for the most part carried out in presence of excess of the aryl magnesium chloride.

The process of the invention may also be carried out by heating the magnesium, arylchloride and boric acid triester in the reaction medium. The reaction temperature employed should be sufficiently high to promote formation of the arylmagnesium chloride, preferably at least 130° C. The boric acid ester used should also have a suitably high boiling point and tri-*n*-butyl borate is therefore particularly suitable. If desired, a reaction initiator may be added to promote formation of the Grignard compound.

The process of the invention is carried out in the absence of hydroxylic compounds such as water or alcohols which will react with the Grignard reagent. Preferably, also, it is carried out in the absence of atmospheric oxygen, suitably in an atmosphere of nitrogen. The reaction mixtures should preferably be stirred vigorously throughout.

The products obtained by the process of the invention are aryl boronic and diaryl borinic esters. When these are esters of aliphatic alcohols of 1 to 4 carbon atoms they may be separated from the reaction mixture

by fractional distillation under reduced pressure after first removing the reaction medium by distillation.

Preferably, however, the reaction mixture is treated with dilute aqueous acid solution to hydrolyse the esters to boronic and borinic acids, the solvent and aqueous layers are separated and the solvent layer is evaporated, eventually under reduced pressure. This method constitutes an extension of the process of the invention. After removing the solvent and the volatile components from the extract the residual arylboron acids may be distilled under reduced pressure or may be recrystallised from an aqueous or aqueous-alcoholic medium. Diarylborinic acid may be separated from the aryl-boronic acid by solution in light petroleum in which the borinic acid has substantially higher solubility. Alternatively, the borinic acid may be isolated as an alkanolamine ester, for example, as the ethanolamine ester, which is insoluble in water.

Alternatively, after removing the solvent and volatile components from the extract as described above, a volatile solvent capable of forming an azeotrope with water is added to the residual arylboron acids, and distillation is continued until the arylboron acids have been completely dehydrated to the anhydrides.

The following examples illustrate the process of the invention, the parts by weight (w) and parts by volume (v) bearing the same relation as the kilogram bears to the litre.

EXAMPLE I.

Preparation of anhydrides of phenylboronic acid and diphenylborinic acid.

Magnesium turnings (13.6 w; 0.56 atom) were placed in a reaction vessel fitted with a dropping funnel, sealed stirrer, reflux condenser (capped by a calcium chloride drying tube) and inlet admitting nitrogen. About one-third of a solution of chlorobenzene (56.4 w; 0.5 mol.) in dry redistilled xylene (170 v) was added together with a crystal of iodine. The reaction mixture was stirred and heated to reflux temperature. The iodine colour disappeared and the solution slowly became opalescent. The remainder of the chlorobenzene solution was then added over a period of one hour and the whole refluxed for four hours. After adding xylene (180 v) to reduce the viscosity and allow unchanged magnesium to settle, the Grignard suspension was poured off into a dropping funnel. It was added gradually at -30°C. to a solution of methyl borate (60.0 w; 0.58 mol.) in xylene (160 v) contained in a reaction vessel fitted with a sealed stirrer, dropping funnel, calcium chloride tube and inlet admitting nitrogen. When addition was complete, the mixture was stirred for two hours before

hydrolysing at 10°C. with 20% sulphuric acid (300 v). The two solvent layers were separated and the aqueous layer was extracted twice with xylene (60 v). The combined xylene extracts were stripped, finally under vacuum. The semi-solid residus was washed twice with light petroleum (b.p. $70-95^{\circ}\text{C.}$; $2 \times 50\text{ v}$) to give phenylboronic acid anhydride as a white powder (8.4 w) of 92% purity.

EXAMPLE II.

Preparation of phenylboronic acid and diphenylborinic acid anhydrides.

Magnesium turnings (24.3 w; 1 atom) and chlorobenzene (675 w; 6 mol.) were heated under reflux for 23 hours. The reaction mixture was decanted from unreacted magnesium and diluted with chlorobenzene to give 1920 w of a solution containing 6.2% w/w of phenylmagnesium chloride. Pure methyl borate (31.2 w; 0.30 mol.) was dissolved in twice its volume of chlorobenzene and cooled to -45°C. in a reaction vessel fitted with condenser capped by a calcium chloride tube, sealed stirrer, dropping funnel, thermometer and inlet admitting nitrogen. A portion of the Grignard solution (554 w, equivalent to 34.2 w or 0.25 mol. PhMgCl) also cooled to -45°C. , was then added with stirring to the methylborate solution. When addition was complete, the mixture was allowed to stand for one hour. The mixture was then poured into a slight excess of 5% w/v sulphuric acid keeping the temperature below 20°C. The chlorobenzene layer was separated from the aqueous layer. The chlorobenzene layer was washed with water (150 v) and evaporated to dryness, eventually at 100°C. and 30 mm. mercury pressure. The crude product was dissolved in ether and extracted with 10% aqueous sodium hydroxide solution. The alkaline extract was washed twice with ether using 50 v each time, then acidified with sulphuric acid (110 v of 2N. H_2SO_4) and the aqueous mixture was extracted four times with ether using 50 v each time. The ethereal extracts were separately evaporated to dryness, finally at 100°C. and 30 mm. mercury pressure. The residue from the first extract (10.4 w) had an acid value of 410 mg of potassium hydroxide per gram and m.p. about 155°C. The second extract yielded 1.4 w of residue of acid value 515 mg of potassium hydroxide per gram and m.p. $206-8^{\circ}\text{C.}$

The aqueous layer separated from the chlorobenzene layer, together with the water washings of the chlorobenzene layer, were extracted twice with ether using 75 v each time and the ether extracts were bulked and evaporated to dryness, finally at 100°C. and 33 mm. mercury pressure giving 4.4 w of

residue with acid value 530 mg potassium hydroxide per gram and m.p. 209—210° C.

The total yield of organoboron compounds obtained was equivalent to 67% of the theoretical amount based on phenylmagnesium chloride used. The yield of phenylboronic acid anhydride (PBO) was 38% and the yield of diphenylborinic acid anhydride (P_2BO) was 29%. Ratio of P_2BO to PBO = 0.76.

In a similar experiment using a reaction temperature of 20° C., the total yield of organoboron compounds was 44% of theory and the P_2BO : PBO ratio was 1.0.

When the reaction was carried out at reflux temperature, the total yield was 50% of theory and the P_2BO : PBO ratio was 3.55.

It can be seen that yields of phenyl boronic acid anhydride which approach 40% of theory can be obtained by employing a reaction temperature of -45° C., but as this temperature is raised, formation of the diphenylborinic acid anhydride is favoured at the expense of the boronic derivative.

EXAMPLE III.

Preparation of anhydrides of phenylboronic acid and diphenylboronic acid.

Four preparations were carried out in which quantities of magnesium turnings and chlorobenzene were refluxed with *n*-butyl borate in the proportions stated in the following table. The reactants, together with a crystal of iodine, were placed in a reaction vessel fitted with sealed stirrer, inlet admitting nitrogen and reflux condenser with calcium chloride tube. The system was flushed with nitrogen and the mixture heated with stirring until refluxing commenced. Reaction set in after about 0.5 hours and was allowed to proceed for the required period of time. It was then cooled (in nitrogen atmosphere) and to the viscous mass an excess of 1.3 N sulphuric acid was added with stirring. The layers were separated and the chlorobenzene layer washed with a little water. It was then heated on a steam bath at 200 mm. mercury pressure to remove the bulk of the butanol and the residue then worked up as described in Example II.

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TABLE.

		A		B		C		D	
EXPERIMENTAL CONDITIONS									
Mg		g. atom		0.705		0.4		0.4	
PhCl		mole/g. atom Mg		9.0		9.0		9.0	
55	B(OBu) ₃	mole/g. atom Mg		0.30		1.2		1.2	
Reaction time hr.		18.0		21.0		4.0		20.5	
PRODUCT									
Aqueous phase ^b									
Wt.		g.		0.1		<0.1		0.1 ^c	
60	Chlorobenzene phase								
Wt.		g.		11.7 4.3		15.8 2.2		10.1 3.0	
Acid value		mg. KOH/g.		346 411		435 523		329 500	
M. pt.		° C.		— —		193—195 196—202		— 180—185 181—189	
YIELD ^d									
65	PBO	% theory		13 ^a		25		6	
P ₂ BO		% theory		36 ^a		23		31	
Total		% theory		49 ^a		48		37	
								22	

a. Yield based on borate.

b. Acid values and M. Pts. not carried out on products from aqueous phase.

c. Sweet smelling liquid.

d. Based on Mg.

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In preparation A after 18 hours reaction time, a yield of 49% (based on borate) of mixed anhydrides ($P_2BO : PBO = 2.78$ w/w) was obtained. The use of a 20% by weight excess of borate in preparation B resulted in a similar combined yield of anhydrides (48% theory) but the proportion of phenylboronic acid anhydride in the product was considerably higher ($P_2BO : PBO = 0.91$). By allowing only 4 hours reaction time in C, the combined yield was 37% theory but the product was largely diphenylborinic acid anhydride ($P_2BO : PBO = 5.26$). In D, the use of a 400% excess of borate lowered the $P_2BO : PBO$ ratio to 0.72 and the combined yield was 22% although a long reaction period was allowed.

EXAMPLE IV.

Preparation of diphenylborinic acid and its 2-aminoethyl ester.

Chlorobenzene (1012.5 w; 9 mol.), magnesium (48.6 w; 2 at.) and isobutylborate (230 w; 1 mol.) were placed in a dry closed vessel (2000 v.) fitted with reflux condenser with calcium chloride tube, an efficient stirrer and a dropping funnel and inlet admitting nitrogen and then heated to reflux temperature. Reaction was initiated by adding a crystal of iodine and a millilitre of ethyl bromide and reaction started in a few minutes. The iodine colour disappeared and a gelatinous product separated from the solution. Reaction was complete after about 4 hours. All the magnesium had then reacted. Dilute hydrochloric acid (200 v. concentrated HCl in 400 v water) was then added to hydrolyse the Grignard compound, the organic layer was separated and the aqueous layer was extracted once with ether (300 v). The organic solutions were combined and dried over anhydrous magnesium sulphate and the solvents distilled off on the water bath under 15 millimetres mercury pressure. In this way, ether, chlorobenzene and butanol were removed. The residue was then distilled under 0.3 to 0.8 millimetres of mercury pressure until imminent decomposition of the residue, 177 w of distillate and 33 w of residue then being obtained. The bulk of the distillate (134 w.) boiled in the range 98° to 120° C. at 0.8 mm. of mercury pressure. There was a fore-run of about 20 w boiling at 60 to 98° C. at 0.8 mm. mercury pressure and a higher fraction of about 24 w boiling at 130° to 190° C. at 0.3 mm. mercury pressure which became semi-solid towards the end.

The total distillate was mixed with a solution of ethanolamine (50 w) in ether (300 v) when there was an immediate precipitate. This was filtered off, washed with ether and dried (120 w; m.p. 172° C.). After recrystallisation from 30% aqueous isopropanol 96 w of pure 2-aminoethyl diphenylborinate, m.p. 188 – 190° C. was obtained. (Yield 42.7%.)

A preparation carried out as described above but with *n*-propyl borate instead of isobutyl borate and a reaction time of 5 hours, gave a 38% yield of the borinate. Another preparation in which xylene was used as solvent in place of excess chlorobenzene and a reaction time of about 20 hours was used gave a 45% yield of the borinate.

WHAT WE CLAIM IS:—

1. A process for preparing arylboron compounds which comprises reacting an arylmagnesium chloride with a boric acid triester in a reaction medium comprising an excess of the aryl chloride from which said aryl magnesium chloride is derived, or a hydrocarbon, to produce the corresponding aryl boronic acid ester, or diarylborinic acid ester or a mixture thereof.

2. A process as claimed in Claim 1, wherein the reaction medium comprises a mixture of said aryl chloride and hydrocarbon.

3. A process as claimed in Claim 1 or 2, wherein the arylmagnesium chloride is derived from a mono- or poly-nuclear aryl chloride containing at least one nuclear chlorine atom.

4. A process as claimed in Claim 3, wherein the arylchloride is substituted by an alkyl, alkoxy, aryloxy, aryl, alkaryl or nitro group, or by a halogen atom.

5. A process as claimed in Claim 3, wherein the aryl chloride is chlorobenzene.

6. A process as claimed in any one of the preceding claims, wherein the boric acid triester is derived from an aliphatic alcohol of 1 to 5 carbon atoms.

7. A process as claimed in any one of the preceding claims, wherein an aromatic hydrocarbon is used as reaction medium.

8. A process as claimed in Claim 7, wherein a xylene or a mixture of xylenes is used as reaction medium.

9. A process as claimed in any one of the preceding claims, wherein approximately one equivalent of the aryl magnesium chloride is reacted with from 1 to 1.3 equivalents of the boric acid triester to produce a product comprising predominantly the aryl boronic acid ester.

10. A process as claimed in Claim 9, which is effected at a temperature below -30° C.

11. A process as claimed in any one of Claims 1 to 10, wherein formation of arylboronic acid ester is favoured by adding the arylmagnesium chloride to the boric acid triester.

12. A process as claimed in any one of Claims 1 to 8, wherein approximately 2 equivalents of the aryl magnesium chloride are reacted with one equivalent of the boric acid triester to produce a product comprising predominantly the diaryl borinic acid ester.

13. A process as claimed in Claim 12,

which is effected at a temperature between 130° and 250° C.

14. A process as claimed in any one of Claims 1 to 8 or 12 or 13, wherein formation of diarylborinic acid ester is favoured by adding the boric acid triester to the aryl magnesium chloride.

15. A process as claimed in any one of Claims 1 to 9, or 11, 12 or 13, which comprises heating the magnesium, aryl chloride and boric acid triester together in said reaction medium at a temperature of at least 130° C.

16. A process as claimed in Claim 15, wherein a reaction initiator is added to the mixture to promote formation of the aryl magnesium chloride.

17. An extension of the process claimed in any one of the preceding claims, wherein the arylboron esters of aliphatic alcohols of 1 to 4 carbon atoms are separated from the reaction mixture by distillation under reduced pressure after first removing the reaction medium by distillation.

18. An extension of the process claimed in any one of Claims 1 to 16, which comprises treating the reaction mixture with a dilute aqueous acid solution to hydrolyse the arylboron esters to arylboron acids, separating the solvent and aqueous layers and evaporating the organic solvent layer.

19. An extension of the process claimed in Claim 18, wherein the residual organoboron acids are distilled under reduced pressure or are recrystallised from an aqueous or aqueous alcoholic medium.

20. An extension of the process claimed

in Claim 18, wherein the residue obtained on evaporating the solvent layer is mixed with a volatile solvent capable of forming an azeotrope with water and the mixture is distilled until the arylboron acids have been converted to the anhydrides.

21. An extension of the process claimed in Claim 18, 19 or 20, wherein diarylborinic acid is separated from arylboronic acid by extraction with light petroleum.

22. An extension of the process claimed in Claim 18, 19 or 20, wherein the diarylborinic acid is separated from arylboronic acid by treating the aqueous or aqueous alcoholic solution with an alkanolamine to precipitate the alkanolamine diarylborinate.

23. A process as claimed in Claim 22, wherein the alkanolamine is ethanolamine.

24. A process as claimed in any one of the preceding claims, substantially as hereinbefore described with reference to the examples.

25. Arylboronic and diarylborinic acids, anhydrides and esters whenever prepared by the process claimed in any one of the preceding claims.

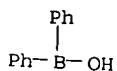
26. Phenylboronic and diphenylborinic acids, anhydrides and esters whenever prepared by the process claimed in any one of Claims 1 to 25.

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AB Arylboron compds. are prepd. by treating an arylmagnesium chloride with a boric acid triester. In an example Mg turnings 13.6 parts were treated under anhyd. conditions under N with a soln. of PhCl 56.4 in dry redistd. xylene 170 parts by vol. together with a crystal of iodine. The mixt. was stirred and refluxed 5 hrs. Xylene 180 was added and the resulting Grignard suspension added slowly to a soln. of 60 parts Me borate in 160 parts by vol. xylene at -30.degree. under N and anhyd. conditions. The mixt. was stirred 2 hrs., then hydrolyzed at 10.degree. with 20% H2SO4 300 parts. Extn. of the aq. layer with xylene gave phenylboronic acid anhydride. In other examples Pr borate, Bu borate, and iso-Bu borate were used. The 2-aminoethyl ester of diphenylborinic acid was also prepd.